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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/535	A1	(11) International Publication Number: WO 99/52531 (43) International Publication Date: 21 October 1999 (21.10.99)
(21) International Application Number: PCT/US99/04289 (22) International Filing Date: 2 April 1999 (02.04.99) (30) Priority Data: 60/081,231 9 April 1998 (09.04.98) US (71) Applicant (for all designated States except US): PHARMACIA & UPJOHN COMPANY [US/US]; 301 Henrietta Street, Kalamazoo, MI 49001 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): HASSAN, Fred [US/US]; 95 Corporate Drive, Bridgewater, NJ 08807 (US). McCALL, John, Michael [US/US]; 1128 North Eagle Lake Drive, Kalamazoo, MI 49009 (US). TAYLOR, Duncan, Paul [US/US]; 8722 West F Avenue, Kalamazoo, MI 49009 (US). VON VOIGTLANDER, Philip, F. [US/US]; 1 South Lake Doster, Plainwell, MI 49080 (US). WONG, Erik, Ho, Fong [US/US]; 7352 Hampstead Lane, Portage, MI 49024 (US). (74) Agent: WOOTTON, Thomas, A.; Pharmacia & Upjohn Company, Intellectual Property Legal Services, 301 Henrietta Street, Kalamazoo, MI 49001 (US).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: NEW TREATMENTS FOR NERVOUS DISORDERS (57) Abstract This patent application describes the treatment of Addictive disorders, Psychoactive Substance Use disorders, Intoxication disorders, Inhalation disorders, Alcohol addiction, Tobacco addiction and or Nicotine addiction; and Attention Deficit Hyperactivity Disorder (ADHD); comprising administering a therapeutically effective, nontoxic dose of Reboxetine and derivatives and or pharmaceutically acceptable salts thereof to a patient.		

 USSN 10/602,447 Filed June 24, 2003
 Docket No. 00054,US1 (PC24974A)

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NEW TREATMENTS FOR NERVOUS DISORDERS

Field of the Invention

5 This invention describes new treatments for several nervous system disorders, including: Addictive Disorders, Psychoactive Substance Use Disorders, Nicotine Addiction or Tobacco Addiction resulting in Smoking Cessation and Attention Deficit Hyperactivity Disorder (ADHD). The treatment involves the administration of the drug Reboxetine to a patient in need.

10 **Background**

The introduction of tricyclic antidepressants in the early 1960s has provided a major advance in the treatment of neuropsychiatric disorders. Reactive and endogenous depressions, diagnoses formerly carrying grave prognostic implications, have become, with the introduction of the tricyclics, manageable disorders with a much smaller toll on the patient and the society as a whole. Electroconvulsive Shock Therapy once the only efficacious treatment in spite of its highly invasive nature, has now become, thanks to tricyclics, an obsolete form of treatment in most Countries.

The early tricyclic compounds were reuptake inhibitors of all the catecholamines released in the synaptic cleft, thus resulting in prolongation and enhancement of the dopamine (DA), noradrenaline (NA) and serotonin (5-hydroxytryptamine = 5-HT) action. Desipramine, for example, has been characterized as “one of the most studied of the tricyclic anti-depressants in ADHD children and adolescents.” T. E. Wilens, et al. *Am. J. Psychiatry* 153:1147-1153, 1148 (1996). It has also been considered as a treatment for the disease in adults. *Id.* Unfortunately, a lack of selectivity for most tricyclics, including desipramine can also cause undesired side effects particularly on the acetylcholine (especially the muscarinic component), and histamine mediated neurotransmission.

Because of these unwanted pharmacodynamic activities, cognitive impairment, sedation, urinary and gastrointestinal tract disturbances, increased intraocular pressure were limiting factors in the clinical use of these compounds and often required discontinuation of treatment. Of utmost concern were also the cardiac toxic effects and the proconvulsant activity of this group of drugs.

Another drug, methylphenidate, is also known to have clinical efficacy for the treatment of ADHD. Wender, P.H., et al. *Am. J. Psychiatry* 142:547-552 (1985).

More recently, selective reuptake inhibitors for serotonin (SSRI) have been introduced with definite advantages in regard to fewer side effects without loss of efficacy.

Here we present the surprising finding that one particular drug from a new category of antidepressants, a so called noradrenaline (NA) reuptake inhibitor can be used to manage
5 or treat a few special diseases, diseases having symptoms outside of what are usually considered depression symptoms. Now these diseases may be treated with Reboxetine.

Summary of the Invention

This patent application describes the treatment of Addictive Disorders, Psychoactive Substance Use Disorders, Nicotine Addition or Tobacco Addiction (with a result of
10 Smoking Cessation or a decrease in smoking) and Attention Deficit Hyperactivity Disorder (ADHD), comprising administering a therapeutically effective, nontoxic dose of Reboxetine and derivatives and or pharmaceutically acceptable salts thereof to a patient.

Reboxetine is the generic name of the pharmaceutical substance with the chemical name of 2-(I-((2-ethoxyphenoxy)benzyl)-morpholine, and its pharmaceutically acceptable
15 salts. Reboxetine can be a free base, or it can include reboxetine methanesulfonate (also called reboxetine mesylate) or any other pharmaceutically acceptable salt that does not significantly affect the pharmaceutical activity of the substance.

A preferred dose range is 4 to 10 mg per patient per day and the most preferred dose is 6 to 8 mg or 8 to 10 mg per patient daily, depending upon the patient, delivered
20 twice a day (b.i.d.).

Additional Description of the Invention and Description of the Preferred Embodiment(s)

Reboxetine is the generic name of the pharmaceutical substance with the chemical name of 2-(I-((2-ethoxyphenoxy)benzyl)-morpholine, and its pharmaceutically acceptable
25 salts. Reboxetine can be a free base, or it can include reboxetine methanesulfonate (also called reboxetine mesylate) or any other pharmaceutically acceptable salt that does not significantly affect the pharmaceutical activity of the substance. Reboxetine and a method of synthesis are described in U.S. 4,229,449, issued 21 Oct. 1980, Melloni et. al., incorporated by reference, methods of preparation are described in US 5,068,433, issued 26
30 Nov. 1991, Melloni et. al. and in US 5,391,735, issued 21 Feb. 1995, both incorporated by reference. Reboxetine may also be known under the trade name of EDRONAX™.

The pharmaceutical compositions and methods of administration described in US 4,229,449 at col. 18, lines 33-66 are specifically incorporated by reference. Twice a day dosing is preferred with current formulations.

Reboxetine acts as an antidepressant. Antidepressants are frequently grouped into categories or "generations." The first generation of antidepressants were usually tricyclic antidepressants such as maprotiline that affected various neurotransmitter systems and are associated with many undesirable side effects. The second generation of antidepressants, such as mianserine, mirtrazapine and trazodone are largely devoid of anticholinergic action and their adrenergic and antihistaminic effects are weaker. These are contrasted with the third generation of antidepressants (e.g. SSRI, ipsapirone, viloxazine, reboxetine, bupropione) that mediate only one of the three main neurotransmitter system for depression (5-HT, noradrenaline, dopamine) and they do not affect muscarine, histamine and adrenergic cerebral systems. Svestka, J. "Antidepressives of the 3rd, 4th and 5th generation," *Cesk-Psychiatr.* 1994 Feb; 90(1):3-19. (Czech).

Reboxetine however; does not act like most antidepressants. Unlike tricyclic antidepressants and even selective serotonin reuptake inhibitors (SSRIs), reboxetine is ineffective in the 8-OH-DPAT hypothermia test, indicating that reboxetine is not a selective serotonin reuptake inhibitor rather it is selective for the noradrenergic system. Thus, reboxetine is not an SSRI, rather it is considered a novel, selective, noradrenaline-reuptake inhibitor (NARI). Leonard-BE, "Noradrenaline in basic models of depression." *European-Neuropsychopharmacol.* 1997 Apr; 7 Suppl 1: S11-6; discussion S71-3. Unlike most drugs, Reboxetine is a highly selective norepinephrine uptake inhibitor, with only marginal serotonin and no dopamine uptake inhibitory activity. The compound displays only weak or no anti-cholinergic activity in different animal models and is devoid of monoamine oxidase (MAO) inhibitory activity.

Reboxetine is highly potent and fast acting. Our investigations indicate Reboxetine has potent antireserpine activity and combines the inhibitory properties of classical tricyclic antidepressants on the reuptake of noradrenaline with an ability to desensitize J-adrenergic receptor function without showing any appreciable interaction with muscarinic cholinergic and I-adrenergic receptors. Moreover, Reboxetine shows less vagolytic activity than other tricyclic antidepressants.

The inventors have discovered that, because of its unique properties, Reboxetine has been found particularly useful for treating or enhancing the treatment of a few psychiatric

symptoms or disorders, with greater efficacy and with fewer side effects, than are treated by known drugs. Furthermore, the inventors here have also discovered that Reboxetine can also be used to treat or to enhance the treatment of a few other specific psychiatric symptoms or disorders. The symptoms or disorders amenable to treatment with Reboxetine
5 are provided below.

The dosage used to treat all of the disorders described here is as follows.

Reboxetine is well tolerated and has a wide safety range, it can be administered in a dose range of active ingredient from about 1 to over 20 mg/kg. It is more commonly provided in dosages of from 1 to 20 mg per patient per day. The compound may be administered by any
10 suitable method including a convenient oral dosage form. A preferred method is oral dosing twice a day. The preferred dose range is 4 to 10 mg per patient per day and the most preferred dose is 6 to 8 mg or 8 to 10 mg per patient daily, depending upon the patient, delivered twice a day (b.i.d.). It can also be given at dosages of 2, 4, 6, 8, 10 or 12 mg per patient per day or fractions thereof. For example, suitable administrations could be 4 mg in
15 the morning and 2 or 4 mg in the evening or 6 mg in the morning and 4 mg in the evening. In some patients the ideal dosing would be 3-5 mg in the morning and 3-5 mg in the evening. A skilled practitioner would be expected to determine the precise level of dosing. The ideal dosing would be routinely determined by an evaluation of clinical trials and the needs of the patient.

20 The diseases described for treatment here are:

I. Addictive Disorders and Psychoactive Substance Use Disorders, such as Intoxication disorders, Inhalation disorders, Alcohol addiction, Tobacco Addiction and or Nicotine Addiction. Tobacco and Nicotine addiction would be treated with the goal of achieving either Smoking Cessation or Smoking Reductions.

25 Addictive Disorders, Alcohol and Other Psychoactive Substance Use Disorders, disorders related to Intoxication and Inhalants and especially Tobacco Addiction or Nicotine Addiction, may be treated with Reboxetine. Tobacco Addiction or Nicotine Addiction would be treated with Reboxetine in order to achieve smoking/chewing cessation or smoking/chewing reduction. General descriptions of Addictive Disorders, including
30 disorders related to Intoxication and Inhalants and Tobacco Addiction or Nicotine Addiction may be found in many standard sources, such as, The American Psychiatric Press Textbook of Psychiatry, Second Edition, Edited by Robert E. Hales, Stuart C. Yudofsky, and John A. Talbott, copyright 1994, incorporated by reference, especially pp. 401 et. seq.,

section on "Nicotine" incorporated by reference. Another of many texts is the Manual of Psychiatric Therapeutics, Second Edition, edited by Richard I. Shader, incorporated by reference, especially pp. 85 from Chapter 11 (Hypnosis).

The treatment of Alcohol and Other Psychoactive Substance Use Disorders, such as disorders related to Intoxication and Inhalants and Tobacco Addiction or Nicotine Addiction but especially Tobacco Addiction involves the administration of Reboxetine in a manner and form that provide a reduction in the symptoms of the disease. Tobacco Addiction or Nicotine Addiction in particular would be treated to achieve a reduction or cessation of smoking or chewing of nicotine containing materials by a patient. Cessation or a reduction in smoking or chewing of addictive or psychoactive substances involves the administration of Reboxetine in a manner and form that provide a reduction in the symptoms of the disease, or with Tobacco or Nicotine with a reduction in the amount smoked or chewed.. See the general description above for administration of Reboxetine.

II. Attention Deficit Hyperactivity Disorder (ADHD).

ADHD is a condition or disease state that may be treated with Reboxetine. General descriptions of ADHD, may be found in many standard sources, such as, The American Psychiatric Press Textbook of Psychiatry, Second Edition, Edited by Robert E. Hales, Stuart C. Yudofsky, and John A. Talbott, copyright 1994, incorporated by reference, especially pp. 741 et. al., section on "ADHD," incorporated by reference. Another of many texts is the Manual of Psychiatric Therapeutics, Second Edition, edited by Richard I. Shader, incorporated by reference, especially Chapter 18, Attention-Deficit hyperactivity Disorder, and pp. 172 et. seq., incorporated by reference.

The treatment of Attention Deficit Hyperactivity Disorder in children and adults involves the administration of Reboxetine in a manner and form that provide a reduction in the symptoms of the disease. A child or young adult may require a smaller dosage depending upon the size, age, condition of the patient. See general description above for administration of Reboxetine.

Claims

1. A method of treating or enhancing the treatment of a disorder selected from:
 - a) Addictive Disorders, Psychoactive Substance Use Disorders, Intoxication disorders,
5 Inhalation disorders, Alcohol addiction, Tobacco Addiction and or Nicotine Addiction; and
 - b) Attention Deficit Hyperactivity Disorder (ADHD);
comprising administering a therapeutically effective, nontoxic dose of Reboxetine and
derivatives and or pharmaceutically acceptable salts thereof to a patient.
- 10 2. The method of claim 1 where Reboxetine is used to treat or enhance the treatment of Tobacco and or Nicotine Addiction.
3. The method of claim 2 where Reboxetine is used to reduce the craving for Tobacco or Nicotine containing products.
- 15 4. The method of claim 2 where Reboxetine is used to reduce the smoking or chewing of Tobacco or Nicotine containing products.
5. The method of claim 1 where Reboxetine is used to treat or enhance the treatment of
20 Attention Deficit Hyperactivity Disorder (ADHD).
6. The method of claim 5 where Reboxetine is used to increase the attention span and calm individuals afflicted with ADHD.
- 25 7. A method for treating or enhancing the treatment of a disorder selected from:
 - a) Addictive Disorders, Psychoactive Substance Use Disorders, Intoxication disorders,
Inhalation disorders, Alcohol addiction, Tobacco Addiction and or Nicotine Addiction; and
 - b) Attention Deficit Hyperactivity Disorder (ADHD);
comprising administering a therapeutically effective, nontoxic dose of Reboxetine and
30 derivatives and or pharmaceutically acceptable salts thereof to a patient in need of an
effective treatment thereof.

8. The use of Reboxetine or its pharmaceutically acceptable salts in the manufacture of a medicament to treat:

a) Addictive Disorders, Psychoactive Substance Use Disorders, Intoxication disorders, Inhalation disorders, Alcohol addiction, Tobacco Addiction and or Nicotine Addiction; and

5 b) Attention Deficit Hyperactivity Disorder (ADHD);
and for any of the symptoms of any of those diseases.

9. The method or use in claims 1-8 where the reboxetine dose range is 4 to 10 mg. per patient per day.

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10. The method or use in claims 1-8 where the reboxetine dose range is 6 to 8 mg. per patient per day.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/04289

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/535

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 99 15177 A (ELI LILLY AND COMPANY) 1 April 1999 (1999-04-01) the whole document	1,5-10
Y	EP 0 721 777 A (ELI LILLY AND COMPANY) 17 July 1996 (1996-07-17) the whole document	1,5-10
Y	EP 0 756 869 A (ELI LILLY AND COMPANY) 5 February 1997 (1997-02-05) the whole document	1,5-10
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
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- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

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- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

30 August 1999

Date of mailing of the international search report

13/09/1999

Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/04289

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	GASTFRIEND D.R. ET AL: "Desipramine in the treatment of attention deficit disorder in adolescents" PSYCHOPHARMACOLOGY BULLETIN, vol. 21, no. 1, 1985, pages 144-145, XP002113690 United States the whole document especially last paragraph ---	1,5-10
Y	WO 96 12485 A (ELI LILLY AND COMPANY) 2 May 1996 (1996-05-02) page 5, line 20 page 6, line 26 - page 7, line 20 ---	1-10
Y	EP 0 534 756 A (ELI LILLY AND COMPANY) 31 March 1993 (1993-03-31) page 2, line 33 & 39 ---	1-4,7-10
Y	LEONARD, B.E.: "Noradrenaline in basic models of depression" EUROPEAN NEUROPSYCHOPHARMACOLOGY, vol. 7, no. suppl. 1, 1997, pages s11-s16, XP002113691 cited in the application abstract ---	1-10
Y	DUBINI, A. ET AL: "Do noradrenaline and serotonin differentially affect social motivation and behaviour?" EUROPEAN NEUROPSYCHOPHARMACOLOGY, vol. 7, no. suppl. 1, 1997, pages s49-s55, XP002113692 abstract ---	1-10
A	PLEAK, R.A. ET AL: "Effects of venlafaxine treatment for ADHD in a child" AMERICAN JOURNAL OF PSYCHIATRY, vol. 152, no. 7, July 1995 (1995-07), page 1099 XP002097978 the whole document -----	1-10

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/ 04289

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-7, 9 and 10
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 1-7, 9 and 10
are directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte. onal Application No

PCT/US 99/04289

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9915177	A	01-04-1999	AU 9214498 A EP 0909561 A	12-04-1999 21-04-1999
EP 721777	A	17-07-1996	US 5658590 A AU 688665 B AU 4693896 A BR 9606903 A CA 2209735 A CN 1168095 A CZ 9702145 A FI 972922 A HU 9801283 A JP 10512262 T NO 973170 A PL 321273 A WO 9621430 A	19-08-1997 12-03-1998 31-07-1996 21-10-1997 18-07-1996 17-12-1997 14-01-1998 09-07-1997 28-06-1999 24-11-1998 02-09-1997 24-11-1997 18-07-1996
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